Angiotensin Converting Enzyme (ACE) Inhibitor Class Review

Factors for Selection of a Second Long-Acting ACE Inhibitor for the Department of Defense Basic Core Formulary

Prepared by the Department of Defense (DoD) Pharmacoeconomic Center (PEC) for the 17 Aug 00 meeting of the DoD Pharmacy & Therapeutics (P&T) Committee. Minutes of the DoD P&T Committee meetings are available on the PEC website at www.pec.ha.osd.mil. The PEC would like to thank the Department of Veterans Affairs Pharmacy Benefits Management (VA PBM) Strategic Health Care Group for the use of clinical trial summaries from their 1997 ACE Inhibitor Review (available on the VA PBM website at www.vapbm.org/PBM/reviews.htm).

Background

- Ten angiotensin converting enzyme (ACE) inhibitors are currently marketed in the U.S. Two of these, captopril (BMS/Apothecon brand) and lisinopril (Zestril; AstraZeneca), are currently on the Department of Defense (DoD) Basic Core Formulary (BCF).
- The BCF designations are the result of a DoD/VA pharmaceutical contract for captopril and a DoD contract for lisinopril. The contract for lisinopril was recently renewed. The contract commits DoD to having Zestril on the BCF until Aug 01. All military treatment facilities (MTFs) must have captopril and lisinopril on their formularies and must use the contracted brands of these products exclusively. However, the contracts for captopril and lisinopril do not affect the ability of DoD and/or individual MTFs to add additional ACE inhibitors to the BCF or to individual MTF formularies.
- Captopril, usually given three times daily, is commonly considered to be a short-acting ACE inhibitor, while the other ACE inhibitors, which are given once to twice daily, are relatively long-acting. For the purposes of this formulary decision, the term long-acting will be used to refer to all ACE inhibitors other than captopril.
- There is clinical evidence that the use of ACE inhibitors reduces morbidity and mortality when given to a wide array of patients, including patients with congestive heart failure (CHF), patients with an acute myocardial infarction (MI), post-MI patients with left ventricular dysfunction, and patients at high cardiovascular risk without LV dysfunction or clinical evidence of CHF. In addition, ACE inhibitors have been shown to slow decline in renal function in both hypertensive and normotensive patients with diabetes. However, it is clear that not all patients that could benefit from ACE inhibitors receive them. The percentage of patients hospitalized with CHF that are discharged with an ACE inhibitor prescription is estimated to be 37-73%.[1] Increased utilization of ACE inhibitors in appropriate patients is highly desirable.

Objective

- To provide information that will help the DoD Pharmacy & Therapeutics (P&T) Committee select a second long-acting ACE inhibitor for the BCF.

Methods

- This document presents an overview of available evidence concerning differences between the available ACE inhibitors in respect to their comparable safety, tolerability, efficacy, and other factors that may affect the committee decision. Examples of other factors to be considered are: provider preference/expert opinion, current usage, compliance/convenience issues, and patent expiration considerations.
- The document is intended to give committee members a basic framework in which to evaluate the value of the drugs in relation to the prices offered by drug manufacturers. Prices obtained by Defense Supply Center Philadelphia in response to a request for price quotes for a Blanket Purchase Agreement (BPA) will be presented separately. These prices are dependent on selection of the agent for the BCF.

Executive Summary

Safety

- There do not appear to be any significant differences between ACE inhibitors with regard to rare but serious side effects or other adverse drug reactions. All ACE inhibitors should be avoided in pregnancy. The type and incidence of major drug interactions with the ACE inhibitors do not appear to differ from drug to drug.
- Fosinopril has a dual elimination mechanism and appears to accumulate less in renal failure than other ACE inhibitors. It may offer a slight safety/convenience advantage over the other long-acting ACE inhibitors because it does not require dose adjustment in patients with renal or hepatic failure. The actual clinical significance is unclear. Other ACE inhibitors typically do not require dose adjustment until creatinine clearance (CrCl) is below 30-40 mL/min, and even then dose adjustment is often not necessary.

PEC Conclusion: Fosinopril may offer a slight safety/convenience advantage in patients with renal or hepatic failure due to its lack of dose adjustment requirements.

Tolerability

- The main tolerability issue that causes patients to discontinue treatment with ACE inhibitors is cough. The incidence of cough during clinical trials has been reported to be as high as 12%, although only about 1% of patients in clinical trials actually discontinued ACE inhibitors due to cough. Providers probably stop ACE inhibitors because of cough much more often than truly necessary. Differences in patient populations, methods of collecting patient complaints, the duration of the trials, and the level of suspicion of clinical investigators could cause wide variance in reported incidence and discontinuation rates. Caution should be exercised when comparing one ACE inhibitor to another on the basis of adverse events reported during clinical trials.
- Moexipril, perindopril, and ramipril appear to have a higher incidence of cough based on clinical trial information (see Table 3). However, all or some of the factors mentioned may have affected reporting of adverse events. For example, the incidence and discontinuation rates are highest for ramipril (12% and 4%, respectively), but these numbers are based solely on results from a relatively recent long-term (1-year) study.

PEC Conclusion: There is insufficient evidence to conclude that ACE inhibitors significantly differ in their propensity to cause cough.

Efficacy

- *Hypertension* –All ACE inhibitors are approved for hypertension (HTN) and appear to be similar in efficacy at comparable doses.
- *Renal Disease and Diabetic Nephropathy* – Enalapril, lisinopril, ramipril, and benazepril have been shown to reduce albumin excretion rate (AER) and/or slow decline in renal function. Conclusive evidence for mortality benefits and/or delay in progression to dialysis or transplant is not yet available. This may be a class effect.
- *Congestive Heart Failure (CHF), post-MI, asymptomatic left ventricular (LV) dysfunction* –Table 1 (at the end of the executive summary) compares the indications and major clinical evidence for each drug (except captopril and lisinopril) in the various patient populations in which it has been tested for major indications other than hypertension. No attempt is made to compare the magnitude of the morbidity and/or mortality benefit for various drugs because of differences in patient populations and clinical trial protocols. The term "little or no evidence" refers to the lack of major randomized controlled trials (RCTs). Two systematic reviews, one of 32 randomized RCTs in CHF patients and the other of four large RCTs in patients post MI, reported no evidence of a difference in mortality reduction between ACE inhibitors.
- *Stroke* – Ramipril appears to be the only ACE inhibitor with evidence of a reduction in the risk of stroke in patients at high cardiovascular risk.

PEC Conclusion

- **All long-acting ACE inhibitors appear to be similar in efficacy for hypertension.**
- **Benazepril, enalapril and ramipril appear to have the most evidence of a beneficial effect on renal disease/diabetic nephropathy.**
- **Enalapril and ramipril appear to have the most extensive evidence of reduction in morbidity and mortality in patients with CHF, post-MI, or asymptomatic LV dysfunction. Trandolapril has evidence of reduction in morbidity and mortality in a subset of these patients (LV dysfunction post MI). Fosinopril, quinapril, and perindopril have evidence of a beneficial effect on signs and symptoms of CHF and on disease progression, but lack mortality data. The remaining drugs (moexipril and benazepril) have little or no evidence supporting use in these patient populations.**
- **Ramipril appears to be the only ACE inhibitor with evidence of a reduction in the risk of stroke in patients at high cardiovascular risk.**

Executive Summary (continued)

Other Factors

- *Pharmacokinetics/Pharmacology* – ACE inhibitors may differ with respect to their receptor binding characteristics and/or ability to penetrate various tissues. In vitro studies with ramipril and quinapril have noted differences in the degree of ACE inhibition in various tissues that may be potentially beneficial, but there is as yet no evidence that this is associated with clinically significant differences in therapeutic effect or patient outcomes.
- *Provider Preference/Expert Opinion* – Most providers had no strong preferences among ACE inhibitors. Those expressing a preference most commonly mentioned fosinopril or ramipril. DoD/VA Clinical Practice Guidelines for Hypertension and Diabetes do not recommend any specific ACE inhibitor.
- *Patent Expirations* – The patent for enalapril expires 22 Aug 00. Multiple generics are anticipated to be available very shortly thereafter. The next patent expiration is for lisinopril, in Dec 01.
- *Dosing & Administration / Compliance / Convenience*
  - ACE inhibitors with trough:peak ratios > 50% following once daily dosing (as measured by ambulatory blood pressure monitoring) are believed to give a more consistent blood pressure lowering effect. Long-acting ACE inhibitors with trough:peak ratios > 50% include enalapril, lisinopril, trandolapril and fosinopril; those with trough:peak ratios < 50% include benazepril, perindopril, ramipril and quinapril.[2] ACE inhibitors with a trough:peak ratio < 50% may require BID as opposed to once daily dosing in some patients, which would affect cost of treatment and may affect patient compliance.
  - Benazepril, fosinopril, lisinopril, and trandolapril are FDA approved for once daily dosing in CHF (trandolapril for CHF post MI). However, ramipril achieved mortality benefits in the HOPE study using once daily dosing. In addition, CHF patients are probably more compliant with BID dosing than patients with HTN, which is largely asymptomatic.
  - An additional convenience issue is the availability of dosing formulations suitable for pediatric patients and patients unable to swallow tablets or capsules (e.g., patients receiving medication via feeding tubes). None of the ACE inhibitors are available in liquid form; however, ramipril capsules may be opened and mixed with a beverage or with applesauce.
- *Current Usage / Formulary Status*
  - Usage in DoD (by tabs/caps, as of April 00): lisinopril 65% >> benazepril (13%) = fosinopril (12%) > quinapril (4%).
  - In a survey of 55 USAF MTF pharmacies, 19 (34.5%) had only the BCF agents on their formulary. A total of 19 MTFs (35%) had fosinopril in addition to the BCF agents, while 14 (25%) and 7 (13%) also had benazepril and quinapril, respectively. One facility also had ramipril (2%). Numbers do not add to 100% because five MTFs had more than one additional ACE inhibitor (see Table 15).
- *Current Blanket Purchase Agreements, Incentive Price Agreements, or Contracts*
  - Aside from the contracts for captopril and lisinopril, the manufacturer of benazepril offers DoD MTFs an incentive price agreement for Lotensin (benazepril) and Lotensin HCT (benazepril/hydrochlorothiazide). The incentive price agreement provides a 54% discount to MTFs that have Lotensin/Lotensin HCT on formulary and that purchase each quarter 75% of the previous quarter's purchases. The agreement reduces the per tablet price for benazepril to about $0.15 for participating facilities. The number of facilities participating in the agreement is unknown. If an ACE inhibitor other than benazepril is added to the BCF, there is a potential for the newly added ACE inhibitor to pull market share away from benazepril at facilities participating in this agreement.

PEC Conclusion: The impending release of generic enalapril appears to be the most important factor in the "Other Factors" category.

Table 1: Clinical Trials Showing Evidence of Morbidity and/or Mortality Benefits with Long-Acting ACE Inhibitors

Excludes captopril and lisinopril; see tables in text for summaries of trials and reviews

		Patient Populations				
Drug	**FDA Indication(s)* all drugs indicated for hypertension**	**High CV risk but without LV dysfunction or CHF**	**Asymptomatic LV dysfunction**	**Symptomatic CHF**	**CHF/LV dysfunction post MI**	**Renal Disease / Diabetic Nephropathy**
Benazepril	-	**Little or no evidence**	**Little or no evidence**	**Little or no evidence**	**Little or no evidence**	**AIPRI –** slowed progression in non-diabetic renal disease
Enalapril	Symptomatic CHF (usually with diuretics and digitalis); asymptomatic LV dysfunction (EF 35%)	**Little or no evidence**	**SOLVD-Prevention** – hospitalization for CHF	**SOLVD-Treatment** in pts with symptomatic CHF – in all-cause mortality, hospitalization for CHF; CONSENSUS I in severe CHF – mortality	**V-HeFT II** with patients post MI 120 days, EF<45% - mortality	At least 5 studies included in 2000 meta-analysis – reduction of albumin excretion rate
Fosinopril	Management of heart failure as adjunctive therapy when added to conventional therapy including diuretics ± digitalis	**Little or no evidence**	**Little or no evidence**	**No mortality data** Trials showed improvements in signs and symptoms, exercise tolerance, NYHA classification, hospitalization for worsening CHF	**Little or no evidence**	**Little or no evidence**
Moexipril	-	**Little or no evidence**	**Little or no evidence**	**Little or no evidence**	**Little or no evidence**	**Little or no evidence**
Perindopril	-	**Little or no evidence *** ***EUROPA** trial in progress in patients with stable coronary artery disease	**Little or no evidence**	**No mortality data**	**Little or no evidence**	**Little or no evidence**
Quinapril	Management of heart failure as adjunctive therapy when added to conventional therapy including diuretics and/or digitalis	**Little or no evidence**	**Little or no evidence**	**No mortality data** Trials showed improvements in signs & symptoms, exercise tolerance, NYHA classification, hospitalizations for worsening CHF	**Little or no evidence**	**Little or no evidence**
Ramipril	In stable patients who have demonstrated clinical signs of congestive heart failure within the first few days after sustaining AMI (additional indications recommended by FDA advisory panel)	**HOPE study** composite measure of MI, CVA, death; all-cause mortality; CHF hospitalization; onset of new CHF, need for revascularization	**1 trial in a subset of this population*** ***APRES** trial – patients with angina pectoris & asymptomatic LV dysfunction post invasive revascularization	**AIRE & AIREX Extension study** in pts with clinical signs of CHF post MI Reductions in all-cause mortality severe heart failure, CHF hospitalization	**AIRE & AIREX Extension study** in pts with clinical signs of CHF post MI	**MicroHOPE** substudy in DM pts- nephropathy **REIN & REIN follow-up studies** decline of GFR
Trandolapril	stable patients who have evidence of left-ventricular systolic dysfunction or who are symptomatic from CHF within the first few days after sustaining AMI	**Little or no evidence**	**Little or no evidence**	**TRACE (CHF post MI)** pts with LV dysfunction (EF 35%) post MI all-cause mortality and progression of CHF	**TRACE** pts w/LV dysfunction post MI all-cause mortality and progression of CHF	**Little or no evidence**

Safety

This section does not include captopril.

Rare but Serious Side Effects

Due to the relatively small numbers of patients in clinical trials that experienced these rare but serious side effects and the voluntary nature of the post-marketing adverse event reporting system, it is not possible to determine if there is a statistically or clinically significant difference among drugs with regard to the following rare but serious side effects.

- *Neutropenia/agranulocytosis* – reported in one patient on quinapril, rare occurrence noted with enalapril and lisinopril, no data available for benazepril, fosinopril, moexipril, perindopril, or ramipril.
- *Angioedema* – According to package labeling, the incidence of angioedema during clinical trials ranged from 0.1% with lisinopril, perindopril, and quinapril to 0.9% with ramipril, no data with fosinopril. Angioedema may be more frequent in black patients.
- *Anaphylactoid reactions* other than angioedema have been reported in patients receiving ACE inhibitors during desensitizing treatment with hymenoptera venom while receiving ACE inhibitors (2 patients), dialysis with high-flux membranes, and undergoing low-density lipoprotein apheresis with dextran sulfate absorption.
- *Hepatic failure* – Extremely rare.

Other Adverse Drug Reactions

- *Hypotension* - Transient hypotension may occur with all of the ACE inhibitors, usually after the first dose. It is not a reason to discontinue the medication.
- *Renal failure* –ACE inhibitors can cause renal failure; BUN and Cr must be monitored. Renal failure is more frequent in patients with unilateral or bilateral renal artery stenosis. In long-term clinical trials with ACE inhibitors post myocardial infarction (MI), <3% of patients discontinued treatment because of renal failure.[3]
- *Hyperkalemia* – Most cases of hyperkalemia resolve even with continued therapy and elevations in serum potassium are typically minor. The incidence and discontinuation rate due to hyperkalemia in clinical trials appear similar for all long-acting ACE inhibitors (see Table 2). There are no head-to-head trials from which incidence rates can be obtained; caution should be exercised when comparing package insert information.

Table 2: Incidence of Hyperkalemia with ACE inhibitors
(package insert information)

Drug	Incidence of Hyperkalemia = serum K= ≥0.5 mEq/L >ULN	Discontinuation rate due to hyperkalemia
Benazepril	1% of patients with HTN	No data
Enalapril	1% of patients with HTN; 3.8% with CHF	0.28%
Fosinopril	2.6% of patients with HTN	0.10%
Lisinopril	2% of pts with HTN; 4.8% in pts with CHF	0.10%(HTN) 0.60%(CHF) 0.10%(with MI)
Moexipril	1.3% of patients with HTN	No data given
Perindopril	1.4% of patients with HTN	No data given
Quinapril	2% of patients with HTN	<0.10%
Ramipril	1% of patients with HTN	none
Trandolapril	5.3% of patients with LV dysfunction post MI	no data given

Special Populations

Renal and hepatic failure

- ACE inhibitors are eliminated by renal, hepatic, or both systems. Because active metabolites may accumulate, dosage reductions are typically recommended in patients with renal or hepatic dysfunction[4,5] However, it is unclear whether dosage requirements for patients with renal or hepatic dysfunction actually differ, especially because the hypotensive effects of ACE inhibitors does not necessarily correlate with serum concentrations.[6]

- Fosinopril has a dual elimination mechanism and appears to accumulate less in renal failure than other ACE inhibitors. Concentrations of the active metabolite do not appear to be significantly higher in patients with cirrhosis compared to normal volunteers. Fosinopril apparently does not need to be dose adjusted in renal or hepatic impairment. This potential safety advantage is likely the reason fosinopril is chosen for many formularies, although the actual clinical significance is unclear. Other ACE inhibitors typically do not require dose adjustment in patients with renal failure until creatinine clearance (CrCl) is below 30-40 mL/min, and even then dose adjustment is often not necessary. In addition, the correlation of clinical adverse effects with accumulation of ACE inhibitors is unclear.
- *Pregnancy* - All ACE inhibitors are Pregnancy Category C in the 1st trimester and Pregnancy Category D in the 2nd and 3rd trimester. ACE inhibitors should be avoided in pregnancy, if possible.

Drug Interactions

All ACE inhibitors have potential drug-drug interactions with NSAIDS, lithium, diuretics, and drugs other than ACE inhibitors that also increase serum K+. These occur infrequently and do not appear to differ among ACE inhibitors.

ACE inhibitors and aspirin

- A specific question was asked at the last P&T meeting concerning the drug interaction between the ACE inhibitors and aspirin, a common drug combination. A recent systematic review of individual patient data from 96,712 patients in trials of ACE inhibitor given in the acute phase of MI (<36 hours from onset) concluded that both aspirin and ACE inhibitors are beneficial in acute MI and that the early use of ACE inhibitors is warranted whether or not aspirin is being given.[7] The *first* RCT to address the following questions: *1) are ACE I effective in patients with CHF treated with aspirin and 2) is aspirin indicated in patients with CHF taking ACE I?* started about a year ago. The WATCH (Warfarin-Antiplatelet Trial in Chronic Heart Failure) trial is a randomized, placebo controlled trial that will prospectively evaluate 4500 patients, most already taking an ACE inhibitor, who will be assigned to treatment with aspirin, clopidogrel or warfarin.[8]
- In the meantime, national clinical practice guidelines for the treatment of heart failure[9] state "…in the absence of adequate data from randomized, clinical trials, both ACE inhibitors and aspirin can be safely administered in the early phase of AMI. Because patients with left ventricular dysfunction have a mortality rate of approximately 50% if they experience a new infarction, prevention with aspirin should not be abandoned on the basis of inadequate data."

Tolerability

- The main tolerability issue that causes patients to discontinue treatment with ACE inhibitors is cough.
- Cough is common in patients with CHF due to their CHF (31%). Most CHF studies had a high incidence of cough with or without ACE inhibitor treatment, however only about 1% of patients in clinical studies actually discontinue ACE inhibitors due to cough. Providers probably discontinue ACE inhibitors due to cough much more often than truly necessary. For most patients, the benefits of ACE inhibitors far outweigh the risk of cough.
- The incidence of cough reported in clinical trials with ACE inhibitors could vary depending on: 1) the patient population under study (CHF vs. HTN); 2) the method of collecting patient complaints; 3) the duration of clinical trials included, and 4) the degree of concern and level of suspicion of clinical investigators. The level of suspicion for ACE inhibitor-induced cough could be expected to be higher in more recently conducted trials, and it is possible that some complaints categorized as upper respiratory tract infection or flu-like symptoms in earlier trials are now being categorized as cough. Higher incidence and discontinuation rates can logically be expected in longer trials, since the adverse effect could appear throughout the course of treatment. The willingness of clinical investigators to discontinue ACE inhibitors due to minor coughs that may not be caused by ACE inhibitor therapy would have a direct effect on the rate of discontinuation, as would communications with trial subjects regarding the seriousness of the side effect. Caution should be exercised when comparing one ACE inhibitor to another on the basis of adverse events reported during clinical trials (see Table 3).
- Moexipril, perindopril, and ramipril appear to have a higher incidence of cough based on clinical trial information; however, all or some of the factors identified earlier may have affected reporting and/or patient behavior. The 12% incidence and 4% discontinuation rate for ramipril, in particular, are derived from a relatively recent 1-year trial. **In the absence of head-to-head trials, it does not seem justified to conclude that any one ACE inhibitor has a higher incidence of cough compared to other ACE inhibitors.**

Table 3: Cough incidence and discontinuation rates due to cough in clinical trials
(package insert information unless noted) (NA = not available)

	ACE inhibitor			Placebo		
Drug	**Incidence of cough**	**Discontinuation rate due to cough**	**N**	**Incidence of cough**	**Discontinuation rate due to cough**	**N**
Benazepril	1.2% HTN	0.5%* HTN	NA	5.0% HTN	NA	496 HTN
Enalapril	1.3% HTN 2.2% CHF	0.1% HTN 0.0% CHF	2314 HTN 673 CHF	0.9% HTN 0.6% CHF	NA	230 HTN 339 CHF
Fosinopril	2.2% HTN 9.7% CHF	0.4% HTN 0.8% CHF	688 HTN 361 CHF	0.0% HTN 5.1% CHF	0.0% HTN 0.0% CHF	184 HTN 373 CHF
Lisinopril	3.5% HTN “>1%” CHF	0.7% HTN NA	1349 HTN 407 CHF	1.0% HTN NA	0.0% HTN NA	207 HTN 155 CHF
Moexipril	6.1% HTN	0.7%** HTN	674 HTN	2.2% HTN	NA	226 HTN
Perindopril	12.0% HTN	1.3% HTN	789 HTN	4.5% HTN	0.4% HTN	223 HTN
Quinapril	2.0% HTN 4.3% CHF	0.5% HTN 0.3% CHF	1563 HTN 585 CHF	0.0% HTN 1.4% CHF	NA NA	579 HTN 295 CHF
Ramipril	12.0% HTN 7.6% CHF post MI	4.0% HTN 1.0% CHF post MI	789 HTN NA	1.8% HTN 3.7% CHF post MI	0.4% HTN NA	223 HTN NA
Trandolapril	1.9% HTN 35.0% LV dysfx post MI	0.1% HTN NA	832 HTN 876 LV dysfx post MI	0.4% HTN 22% LV dysfx post MI	0.4% HTN NA	237 873 LV dysfx post MI

* Data on file. Novartis
** Data on file. Schwarz Pharma

Efficacy

Table 4: FDA-approved indications

Generic Name	Trade Name	HTN	CHF	Post-MI	LV dysfunction	DM nephropathy
Benazepril	Lotensin	Yes	No	No	No	No
Enalapril	Vasotec	Yes	Yes	No	Yes♥	No
Fosinopril	Monopril	Yes	Yes**	No	No	No
Lisinopril	Zestril	Yes	Yes**	Yes♥♥	No	No
Moexipril	Univasc	Yes	No	No	No	No
Perindopril	Aceon	Yes	No	No	No	No
Quinapril	Accupril	Yes	Yes**	No	No	No
Ramipril	Altace	Yes	Yes*	No	No	No
Trandolapril	Mavik	Yes	Yes*	Yes♥♥♥	Yes*	No

* post MI
** adjunctive to diuretics with or without digoxin
♥ asymptomatic LV dysfunction
♥♥ within 24 hours to improve survival
♥♥♥ within first few days in patients with symptomatic heart failure or left ventricular dysfunction to improve survival
† An FDA advisory committee has recommended approval of new indications for ramipril for the “significant reduction of cardiovascular death, myocardial infarction, stroke, and "all-cause mortality" in patients at risk for such cardiovascular events.” This new indication is not yet FDA approved.

Clinical Evidence Tables

- This document contains a summary of significant trials compiled from the excellent VA ACE inhibitor review completed in 1997, plus relevant trials completed in the last 3 years. The focus is on the best and most useful clinical evidence; this is not an exhaustive review of all ACE inhibitor trials. The intent is to review the available evidence of long-term benefit (i.e., reductions in morbidity and mortality) for each long-acting ACE inhibitor. Earlier trials with captopril have largely been omitted.

- The VA review is available at: http://www.vapbm.org/PBM/reviews.htm

ACE Inhibitors for Hypertension

- ACE inhibitors appear to work equally well lowering in lowering blood pressure when given in comparable doses. All ACE inhibitors are approved for hypertension. Efficacy trials of ACE inhibitors for hypertension that do not also address other important clinical outcomes or provide post-marketing data are not included in the tables of clinical evidence below.
- ACE inhibitors with trough:peak ratios > 50% following once daily dosing (as measured by ambulatory blood pressure monitoring) are believed to give a more consistent blood pressure lowering effect. This is discussed both under efficacy and compliance, since drugs with trough:peak ratios < 50% may require BID as opposed to once daily dosing. ACE inhibitors with trough: peak ratios > 50% include: enalapril, lisinopril, trandolapril and fosinopril. ACE inhibitors with trough: peak ratios < 50% include: captopril, benazepril, perindopril, ramipril and quinapril.[10] However, many hypertensive patients will still do well on these meds with once daily dosing.

Table 5: ACE I in Patients with Hypertension

(RCT = Randomized controlled trial, SR = systematic review)

Drug	Description of trial, systematic review or meta-analysis	Comments
Enalapril, lisinopril	**STOP**[11] Unblinded, controlled trial comparing diuretics and/or B-blockers *vs*. CA-Channel blockers *vs*. ACE-inhibitors. Published 1999	6600 patients ages 70-84. No significant difference in blood pressure control or cardiovascular morbidity or mortality. Flaw in randomization resulted in unbalanced groups. Overall, 30% of patients receiving enalapril or lisinopril had cough.
Enalapril ± HCTZ, nitrendipine ± HCTZ	RCT (Syst-Eur)[12] (2 years) Outcomes MI, CHF or sudden cardiac death. Pts at least 60 y.o. with isolated systolic HTN (ISH).	Results lumped together. Beneficial to treat ISH with reduction in MI, CHF, sudden death (13/252) 5.2% vs. (31/240) 12.9% (treated vs. untreated patients.) NNT=13. Adverse effects not addressed.
Perindopril	Post marketing surveillance study[13] of 47,351 pts with 4800 general practitioners in France. Tx initiated at 4mg (2mg if >age 70) & ↑ to 8mg max if DBP remained >95. Diuretic added then if still necessary. Open label study.	At 12 months DBP < 90 seen in 68 & 77% of pts on 4 & 8mg, respectively. No unexpected occurrences 1-year post drug appearance on the market. Only 279 patients (0.59%) withdrew due to lack of efficacy. 2401 (5.12%) withdrew due to adverse effects. Cough seen in 9.7% of pts but only 3.3% of patients withdrew due to cough. Renal failure noted in 0.02-0.05% of patients. Orthostatic hypotension in 0.16-1.24% of patients.

ISH = isolated systolic hypertension; NNT = number-needed-to-treat; DBP = diastolic blood pressure

ACE Inhibitors for Congestive Heart Failure (CHF), post-MI and/or in Asymptomatic Left Ventricular Dysfunction

- A 1999 community-based prospective study of 2906 patients found that patients recently hospitalized for CHF remain at high risk of death (5% during index admission, 17% in 6 month follow-up) and recurrent hospital admission (43% for any cause; 25% of those for CHF).[14] Despite recent advances in treatment of CHF, morbidity and mortality remain high whether treatment is community based or in a tertiary care center. The 5-year mortality rate for CHF is similar to many malignancies.
- ACE inhibitors decrease peripheral resistance, reduce afterload (peripheral vascular resistance), preload (pulmonary capillary wedge pressure), pulmonary vascular resistance and heart size, and increase cardiac output and exercise tolerance time in patients with CHF. Clinical trials with ACE inhibitors have demonstrated reductions in morbidity and mortality, reductions in hospitalizations for heart failure, increases in exercise tolerance, and reduction in progression to CHF.
- All of the long-acting ACE inhibitors except benazepril, moexipril, and perindopril are approved for CHF. There are some differences in CHF indications among ACE inhibitors, depending on the nature of the clinical trials.
    - *Enalapril* – "symptomatic CHF, usually in combination with diuretics and digitalis, and in clinically stable asymptomatic patients with left ventricular dysfunction (ejection fraction 35%)." Enalapril has the most clinical evidence of all the ACE inhibitors concerning efficacy in CHF. Trials include SOLVD-Treatment in patients with symptomatic CHF (11% reduction in all–cause mortality; 30% reduction in hospitalization for CHF); SOLVD-Prevention in patients with asymptomatic or minimally symptomatic CHF (32% reduction in hospitalization for heart failure;); CONSENSUS in patients with severe CHF (40% reduction in mortality at 6 months, 27% at 1 year), and V-HeFT II. The mortality benefit in SOLVD-Treatment did not appear to depend on the presence of digoxin.

CONSENSUS II (early treatment with intravenous enalaprilat post MI) was stopped early due to concern over possible early adverse hypotensive events in the elderly.

- *Fosinopril* – "management of heart failure as adjunctive therapy when added to conventional therapy including diuretics with or without digitalis." Package labeling gives combined results of three 12-24 week clinical trials showing favorable effects on exercise tolerance, symptoms of dyspnea, New York Heart Association (NYHA) classification, hospitalization for heart failure, study withdrawals for worsening heart failure, and/or need for supplemental diuretics. No long-term mortality data in CHF.
- *Lisinopril* – "as adjunctive therapy in the management of heart failure in patients who are not responding adequately to diuretics and digitalis." Package labeling refers to results of two 12-week trials showing favorable effects on signs and symptoms, exercise tolerance, NYHA classification. The GISSI-3 trial in patients with acute MI examined the effect of a short-term, post-MI (6-week) course of lisinopril on short- and long-term outcomes. Results: 11% reduction in mortality at 6-weeks, numerical superiority but no conclusion possible at 6 months. Patients on lisinopril had a higher incidence of persistent hypertension and renal dysfunction in hospital and at 6 weeks. No long-term mortality data in CHF.
- *Quinapril* – "management of heart failure as adjunctive therapy when added to conventional therapy including diuretics and/or digitalis." Package labeling refers to results of a clinical trial demonstrating favorable effects on NYHA classification, quality of life, and symptoms of CHF. No long-term mortality data in CHF.
- *Ramipril* – "in stable patients who have demonstrated clinical signs of congestive heart failure within the first few days after sustaining AMI." Trials include AIRE (27% reduction in all-cause mortality, 23% reduction in severe heart failure, 26% reduction in CHF hospitalization in patients with clinical signs of CHF started on ramipril 2-9 days after AMI and followed for a mean of 15 months) and HOPE (22% reduction in composite of MI, CVA, death; 16% all-cause mortality, 23% reduction in onset of new CHF in patients with at high risk for CV events but without overt LV dysfunction or CHF). The 4.5 year HOPE trial and the MicroHOPE substudy also demonstrated reductions in the need for revascularization, development of nephropathy and new microalbuminuria, and development of diabetes.
- *Trandolapril* – "stable patients who have evidence of left-ventricular systolic dysfunction or who are symptomatic from CHF within the first few days after sustaining AMI." TRACE study (Danish) of the effect of trandolapril on all-cause mortality in stable patients with LV dysfunction 3-7 days post MI demonstrated a 16% reduction in risk of all-cause mortality and a 20% reduction in the risk of progression of heart failure, following 24 months of treatment. Generalizability of this trial is problematic, as the population was entirely Caucasian, fewer other post-MI interventions were performed than U.S. norm, and blood pressure control was poor.

Table 6: ACE Inhibitors in Patients with CHF
(RCT = Randomized controlled trial, SR = systematic review)

Drug	Description of trial, systematic review or meta-analysis	Comments
multiple drugs reviewed	Systematic review of ACE inhibitors vs. placebo in CHF (32 RCTs, 7105 pts, ≥NYHA II 3-42 month) published 1995.[15]	Mortality reduction with ACE inhibitors. Review of 32 trials with 7105 patients; 6 with captopril (n=697), 7 with enalapril (n=3381 patients), 6 with ramipril (n=1227 patients), 5 with quinapril (n=875 patients), and 4 with lisinopril (n=546 patients). Benazepril, cilazapril, and perindopril were used in one or two trials involving a total of 379 patients. Death: ACE inhibitors = 611/3870 patients (15.8%); controls = 709/3235 (21.9%). Statistically significant (OR 0.77). Although data for benazepril, cilazapril, and perindopril were limited, no detectable heterogeneity of effect was observed. Findings of this analysis are consistent with results of SOLVD and CONSENSUS II. The SR found similar benefits with different ACE inhibitors, suggesting a class effect of ACE inhibitors (although moexipril was not studied). All RCTs noted a high proportion of people in both TX and placebo groups reporting adverse effects (up to 76% in one RCT)
Benazepril, placebo	Multicenter RCT[16] 172 pts; randomized 2:1 treatment vs. placebo; EF 35%; NYHA II – IV on dig, diuretics	Follow-up 3 months; no risk reduction data Exercise duration mean: benazepril: +95 ± 12 sec from baseline vs. placebo: +37 ± 18 sec (p=0.007) Symptoms of CHF improved by 1 or more NYHA classes: benazepril 31% vs. placebo 15% (p=0.05)

Table 6 continued: ACE Inhibitors in Patients with CHF

Drug	Description of trial, systematic review or meta-analysis	Comments
Enalapril, placebo	**CONSENSUS I**[17] Multicenter RCT 253 pts intention-to-treat trial NYHA IV; EF not available; post MI > 60 d Follow-up range 1 day – 20 mo (mean: 6.3 mo)	Reduced mortality by 40% with enalapril at 6 mo; 27% at end of study Crude mortality 26% vs. 44% with placebo at 6 mo Reduction in progressive CHF 50% Premature termination in favor of enalapril At ten year follow-up[18], risk reduction averaged over duration of trial was 30% (95% CI 11-46%)
Enalapril *vs*. Hydralazine / isosorbide	**V-HeFT II**[19] Multicenter RCT, 804 pts EF < 45%; post MI 120 d Follow-up range 6 months – 5.7 yr	Mortality after 2 yrs significantly reduced with enalapril (18%) vs. combination (25%) (p=0.016); Overall mortality tended to be lower with enalapril (p=0.08)
Enalapril, placebo	**SOLVD-Treatment**[20] Multicenter, RCT; 4569 pts; intention-to-treat in pts > 28 days post MI with EF 35%	Follow-up range: 22 - 55 months (mean: 41.4 months) Mortality risk reduction of 16% with enalapril (p=0.0036) CV death risk reduction: 18% (p<0.002) CHF death risk reduction: 22% (p<0.0045) Hospitalization due to CHF: risk reduction 26% (p<0.0001)
Lisinopril, captopril	Multicenter RCT[21] 387 pts; EF < 45%; NYHA II - III	Follow-up 3 months; no risk reduction data Exercise duration: lisinopril +47.2 sec; captopril +44.3sec 6 wks (p=0.77); exercise tolerance continued to ↑ for both 12 wks (p=0.68) No significant differences between groups Compared to baseline, both treatment groups significantly increased exercise duration at both 6 and 12 weeks
Fosinopril, placebo	Multicenter RCT[22] 241 pts; exclusion with recent MI EF 35%; mean: 25 ± 7% Digoxin discontinued prior to trial	Follow-up 6 months; no risk reduction data Improvement in exercise tolerance: fosinopril +28.4 sec vs. -13.5 sec placebo Hospitalized for worsening CHF: fosinopril (5.2%) vs. placebo (9.6%) Withdrawal for worsening CHF: fosinopril 16 vs. placebo 40
Fosinopri, enalapril	RCT[23] 254 pts randomized to fosinopril 5-20mg qd or enalapril 5-20mg qd for 1-year	Rate of hospitalizations or death reduced with fosinopril: 19.7% fosinopril, 25% enalapril, p=0.028. Incidence of orthostatic hypotension lower with fosinopril (1.6% vs. 7.6%, p < 0.05)
Perindopril, placebo	RCT[24] 125 pts with NYHA Grade II or III CHF on diuretics, 3-month study	Significant increase in exercise time, bicycle and treadmill, with perindopril, improvement in NYHA class (p=0.009), HF severity score (p<0.001). Twelve withdrawals, 2 perindopril and 5 placebo; 1 death in placebo group.
Quinapril, captopril	Multicenter RCT[25] 146 pts; intention-to-treat NYHA I – III, on pre-study dig, diuretics	Follow-up 3 months; no risk reduction data Exercise duration mean: quinapril: baseline 422.1 sec vs. 12 wks 497.2 sec (p<0.05) captopril: baseline 451.7 sec vs. 12 wks 519 sec (p<0.05) *Captopril had more homogeneous distribution NYHA I-III vs. quinapril group which had more NYHA II (p<0.05) No significant difference in results between groups
Quinapril, placebo	Multicenter RCT[26] withdrawal trial in 224 pts EF 35%; NYHA II – III on stable doses dig, diuretics	Follow-up 4 months; no risk reduction data After 10 weeks of single-blind quinapril therapy pts randomized in double-blind fashion to quinapril or placebo Exercise duration mean: quinapril +3sec; from baseline vs. placebo -16 sec NYHA functional class (p=0.004) and quality of life improved & signs and symptoms of CHF lessened in quinapril therapy Therapeutic failures: quinapril 5 pts vs. placebo 18 pts (p<0.001)
Ramipril, placebo	**HOPE**[27] RCT (4.5 years); 9297 pts with vascular disease or DM + one other CV risk factor who did not have LV dysfunction or CHF. Primary outcome a composite of MI, stroke or death from CV causes.	Ramipril reduced risk of primary endpoint: AR 14% ramipril, 17.8% with placebo (RR 0.78, 95% CI 0.70-0.86, p<0.001). Ramipril reduced risk of death from CV causes: AR 6.1% ramipril, 8.1% placebo (RR 0.84). Ramipril reduced risk of CHF *vs*. placebo: AR 9.0% with ramipril, 11.5% with placebo (RR 0.77, 95% CI 0.67-0.87, P<0.001). 7.3% discontinued d/t cough with ramipril, 1.8% with placebo.

RCT = randomized controlled trial; OR = odds ratio; RR = risk ratio; AR = absolute risk; NYHA = New York Heart Association

Table 7: ACE Inhibitors Post-MI and/or in Asymptomatic Left Ventricular (LV) Dysfunction
(RCT = Randomized controlled trial, SR = systematic review)

Drug	Description of trial, systematic review or meta-analysis	Comments
review	SR of 4 large (each >1000 patients) RCTs published in 1998[28]	Participants treated with ACE I within 24 hrs of symptoms of AMI had reduced mortality. Hypotension in both higher and lower CV risk groups.
Captopril, ramipril, trandolapril	SR of 3 RCTs (1997) all vs. placebo 5966 patients with recent MI and LVEF __ 35-40%[3]	ACE I significantly reduced rate of death. (RRR 26%, NNT 17 people for 2 years. Tx also reduced hospitalization for CHF (RRR 27%, NNT 28). Tx also reduced risk of recurrent non-fatal MI (RRR 20%, NNT 43). Cough 5-10% vs. placebo. Dizziness/hypotension 5-10% vs. placebo. Renal failure/hyperkalemia <3%
Enalapril, placebo	**SOLVD-Prevention[29]** Multicenter RCT; 4228 pts; intention-to-treat; EF 35% post MI > 28 d	Follow-up range: 14.6 – 62 months (mean = 37.4 months) Total mortality risk reduction for enalapril: 8% (p=0.30) Development of CHF risk reduction: 29% (p<0.001) Died or hospitalized for new or worsening CHF: 20% (p<0.001)
Enalapril, placebo	**CONSENSUS II[30]** Multicenter RCT 6090 pts enrolled; 2952 pts followed for 6 months; intention-to-treat post MI within 24 hours Proposed: 6 months; actual 41 - 180 days	Early discontinuation of trial due to concern over possible early adverse hypotensive events in elderly; no risk reduction data Death: enalapril (10.2%) vs. placebo (9.4%) (p=0.26) Death due to CHF: enalapril (3.4%) vs. placebo (4.3%) (p=0.06) Change of therapy due to heart failure: enalapril 27% vs. placebo 30% (p=0.006)
Lisinopril ± transdermal glyceryl trinitrate (GTN)	**GISSI-3[31]** Multicenter; randomized open label; 19,394 pts; intention-to-treat EF at 6 weeks; post MI within 24 hours; no patient selection	Follow-up 6 months Mortality risk reduction at 6 weeks with lisinopril 11% (p=0.03); odds ratio 0.88 (0.79-0.99) 6 week combined endpoint (death, clinical heart failure, EF 35%, akinesis, dyskinesis score > 45%): lisinopril 8% reduction (p=0.009); odds ratio 0.90 (0.84-0.98) 6 month combined endpoint: Lisinopril 6% reduction (p=0.03); Odds ratio 0.92 (0.86-0.99) No difference found between patients with and without GTN
Ramipril, placebo	**AIRE Study[32]** Multicenter RCT; 2006 pts with clinical evidence of HF post MI	Mean follow-up 15 months. Study medication started 3-10 days post MI Reduction in all-cause mortality – 170 deaths (17%) ramipril vs. 222 deaths (23%) placebo. Relative risk reduction 27% (95% CI 11-40%; p=0.002)
Ramipril, placebo	**AIRE Extension Study[33]** Objective to determine long term survival benefit of ramipril for CHF post MI 3 years after the end of AIRE study. 603 patients total. 302 got tx: 1.25-2.5mg BID ramipril given 2-9 days post MI and titrated up to 2.5-5mg BID vs. 301 on placebo. All meds dc'd after 15 months and pts tx'd at primary physician's discretion.	At 59 months, there were 83 deaths in ramipril group; 117 deaths in placebo group (p=0.002) Ramipril =28%; placebo =39%. RRR of 36%. ARR = 11%. NNT =9.
Trandolapril, placebo	**TRACE[34]** Multicenter RCT; 1749 pts EF 35%; post MI 3-7 d	Follow-up 24 - 50 months (mean 26); study medication started 3-7 days post MI Relative risk of death in trandolapril group vs. placebo: 0.78 (95 % CI, 0.67-0.91). Total mortality: 34.7% vs. 42.3% placebo; 22% reduction (p=0.001) Progressive CHF: 125 pts vs. 171 placebo 29% reduction (p=0.003) CV deaths: 226 pts vs. 288 placebo; 25% reduction (p=0.001) Sudden deaths: 105 pts vs. 133 placebo; 24% reduction (p=0.03)

RCT = randomized controlled trial; OR = odds ratio; RRR = relative risk reduction; NNT = number-needed-to-treat; ARR = absolute risk reduction; NYHA = New York Heart Association

Table 8: ACE Inhibitors in Diabetics with Cardiovascular Disease

(RCT = Randomized controlled trial, SR = systematic review)

Drug	Description of trial, systematic review or meta-analysis	Comments
Fosinopril	**FACET**[35] RCT (2.9years); open label trial. Purpose to compare effects of fosinopril and amlodipine on lipids and diabetic control in patients with Type 2 DM and HTN. Prospectively defined CV events assessed as secondary outcomes	Outcomes of AMI, stroke, or admission to hospital for angina (14/189) 7.4% in fosinopril group vs. (27/191) 14.1% in amlodipine group. NNT=15 No significant difference found in lipids or glucose control. Amlodipine better for HTN control which raises the discussion of using surrogate endpoints to determine treatment used for patients.
Ramipril, placebo	**MICROHOPE**[36] Substudy of HOPE trial RCT (4.5 years); subgroup of 3577 pts with DM + one other CV event or risk factor who did not have LV dysfunction or CHF. Primary outcome a composite of MI, stroke or death from CV causes.	Significant reduction in primary endpoint compared to placebo: AR = 15.3% ramipril, 19.8% placebo (relative risk reduction of 25%, 95% CI 12-36%, P=0.0004) 7% discontinued tx due to cough with ramipril (2% in placebo group). 1.9% d/c'd tx due to hypotension or dizziness with ramipril (1.5% in placebo group)
Trandolapril, placebo	**Post hoc subgroup analysis of the TRACE data**[37] Of 1749 pts in TRACE, 237 (14%) were DM on retrospective analysis. Of the 237 diabetics, 48.1% received trandolapril. ACE inhibitors in DM pts post MI with LV dysfunction appear to save lives by ↓ing risk of progression to CHF. NNT to save 1 life in 26 months=6 in DM group; 17 in nondiabetic group.	Tx with trandolapril: relative risk of death from any cause in DM group: 0.64 (95% CI 0.45 to 0.91) vs. 0.82 (0.69 to 0.97) for nondiabetic group. Trandolapril reduced risk of progression to severe CHF in DM group: RR 0.38 (0.21 to 0.67) with no significant reduction of this end point in the nondiabetic group During follow-up, 126 (53%) pts died in DM group vs. 547 (36%) in nondiabetic group. 51 (45%) of DM randomized to trandolapril died vs. 75 (61%) of DM randomized to placebo. In nondiabetic group, 253 (33%) tx with trandolapril died vs. 294 (39%) tx with placebo.

RCT = randomized controlled trial; RR = risk ratio; NNT = number-needed-to-treat

ACE Inhibitors in Renal Disease and Diabetic Nephropathy

- Few large, randomized long-term trials evaluating ACE inhibitors in diabetic nephropathy are available. ACE inhibitors appear to decrease albumin excretion rates (AER) and slow decline in renal function in both hypertensive and normotensive diabetics. Evidence of a reduction in mortality and/or delay in progression to dialysis or renal transplant is lacking. The beneficial effects of ACE inhibitors may be independent of their antihypertensive effects. **More than one ACE inhibitor has demonstrated these properties, suggesting that this may be a class effect of ACE inhibitors.**

- ACE inhibitors also appear to delay the progression of renal disease in nondiabetics.

Table 9: ACE Inhibitors in Renal Disease and Diabetic Nephropathy

(RCT = Randomized controlled trial, SR = systematic review)

Drug	Description of trial, systematic review or meta-analysis	Comments
Captopril (5 studies) Enalapril (5 studies) Lisinopril (1 study)	Meta-analysis (11 studies) Initially normotensive diabetics with microalbuminuria.[38]	ACE inhibitor tx can arrest and reduce albumin excretion rate and is accompanied by reduction in BP. Direct link with postponement of ESRD not shown. No substantial side effects noted.

Table 9 continued: ACE Inhibitors in Renal Disease and Diabetic Nephropathy

Benazepril, placebo	**AIPRI**[39] Multicenter RCT 583 pts with CRI defined as sCr 1.5 to 4 mg/dl and a 24-hour estimated CrCl of 30 to 60 ml/min	Follow up 3 yrs Glomerulopathies (n = 192), interstitial nephritis (n = 97), nephrosclerosis (n = 97), polycystic kidney disease (n = 64), diabetic nephropathy (n = 21), and miscellaneous/unknown (n = 104) A total of 88 pts (31 in the benazepril group and 57 in placebo group) reached primary end point (86 pts had doubling of base-line sCr and 2 required dialysis (renal survival significantly better in the benazepril group (p<0.001) Of the pts with diabetic nephropathy 1 of 6 pts in the benazepril group and 7 of 15 in the placebo group reached the primary end point. Overall unadjusted reduction in the risk of progressive renal insufficiency was 53% in the benazepril group. After an adjustment for supine diastolic pressure and AER the reduction in risk was 38 and 39% respectively, a significant difference.
Enalapril, placebo	Multicenter RCT[40] 94 pts with NIDDM, age < 50 yrs old, duration of DM < 10 yrs AER 30 - 300 mg/24 h Normotensive (BP 140/90)	Follow up 5 yrs Risk reduction of 30% (95% CI,15 - 45 p<0.001) 42% pts placebo vs. 12% pts enalapril progressed to clinical proteinuria (AER > 300 mg/24h) AER increased with placebo from 123 ± 58 to 134 mg/24 h in the 1st year and increased to 310 mg/24 h by the 5th year; AER decreased from 143 ± 64 to 122 ± 67 mg/24 h with enalapril and then slowly decreased to 140 ± 134 mg/24 h by the 5th year
Lisinopril, nifedipine SR	Multicenter RCT[41] 335 pts with stable NIDDM for > 3 months; males (18-75 yrs old), postmenopausal females (40-75 years old) with microalbuminuria and incipient nephropathy (UAE 20-300 mg/min)	Follow up 1 yr Lisinopril associated with a fall in median UAE rate of 24.5 mg/min (range -210 to 69 mcg/min) at 6 months and 1mcg/min (range -216 to 397 mcg/min) at 12 months Nifedipine SR associated with a net fall of mcg/min (range -211 to 529 mcg/min) and 2.0 mcg/min (range -195 to 933 mg/min) at 6 and 12 months, respectively.
Ramipril, placebo	MICROHOPE[36] Substudy of HOPE trial, 3577 patients with diabetes 55 y.o. w/1 CV event or risk factor, w/o proteinuria, HF or low EF. Overt nephropathy main substudy outcome	See other tables for combined endpoint results. Reduction in risk of overt nephropathy: AR = 6.5% ramipril, 9.7% placebo (RRR = 37% 95% CI 21-51%, p=0.027) Combined endpoint of overt nephropathy, laser therapy, or dialysis. 15.1% ramipril, 17.6% placebo (RRR=16% (1-29%, p=0.036)
Ramipril, placebo	REIN and REIN followup studies[42,43,44] 352 pts classified by baseline proteinuria: stratum 1 (1-3 g/24h) or 2 (3g/24h) ; randomized to ramipril or placebo + conventional antihypertensives; target DBP < 90 mmHg. Primary endpoint rate of GFR decline in core study; also incidence of ESRF in follow-up	At second planned analysis, highly significant difference in decline between ramipril and placebo in stratum 2 (baseline proteinuria 3g/24h) (p=0.001). Final analysis done for Stratum 2 and all pts on placebo switched to ramipril & recruited for follow-up study. Stratum 1 continued. Decline in GFR per month 0.53 mL/min ramipril, 0.88 mL/min placebo, p=0.03, in Stratum 2. REIN follow-up--mean observation period (core study and follow-up): 23 months (range 4-53 mo). # patients available for final analysis: 26 ramipril, 17 switched to ramipril. Kidney survival (proportion of pts without ESRF during whole study period (core study and follow-up): 19 events on pts continuing ramipril, 35 events on patients initially on placebo (RR = 1.86, 95% CI 1.07-3.26, p=0.03) Follow-up study in Stratum 1 patients (proteinuria 1-3 g/24h): decline in GFR not significantly different; progression to ESRF or overt proteinuria significantly less common with ramipril. Mean follow-up 31 months

RCT = randomized controlled trial; NIDDM = non-insulin dependent diabetes mellitus; ESRD =end-stage renal failure;
AER = albumin excretion rate; AR = absolute risk; RRR = relative risk reduction

ACE Inhibitors for Stroke Prevention

There is little clinical trial evidence at the present time. A major trial, the Peridopril Protection Against Recurrent Stroke Study (PROGRESS) is scheduled for completion in 2001.

Table 10: ACE Inhibitors for Stroke Prevention

(RCT = Randomized controlled trial, SR = systematic review)

Drug	Description of trial, systematic review or meta-analysis	Comments
Ramipril	**HOPE**[27] 9297 pts with vascular disease or DM + one other CV risk factor who did not have LV dysfunction or CHF vs. placebo. Primary outcome a composite of MI, stroke or death from CV causes.	Ramipril reduced stroke risk compared to placebo by 31% and reduced risk of combined outcome of stroke, MI or CV death by 22%. Results were similar with or w/o HTN and with or w/o previous Hx CVA/TIA. Harm not discussed except that there was no evidence of any threshold below which a lower diastolic BP was not associated with a lower stroke risk. No evidence of harm by reducing DBP down to 80.

Other ACE Inhibitor Trials

Table 11: Other ACE Inhibitor Trials

Drug	Description of trial, systematic review or meta-analysis	Comments
Lisinopril	**ATLAS**[45] open label trial comparing effect of high vs. low dose lisinopril (2.5-5mg/d vs. 32.5-35mg/d) on all cause mortality (primary outcome); Nov 99	No significant differences in CV mortality; high dose significantly better in secondary outcomes of all cause hospitalization and mortality and recurrent hospitalization No difference in A/E profile for high vs. low dose. More patients withdrew from low dose group. Problem: intermediate dose range not explored
Quinapril, placebo	**QUIET** trial[46] (Quinapril Ischemic Event Trial) Quantitative coronary angiography (QCA) Prospective RCT to evaluate benefit of ACE I in antiatherosclerotic therapy. 1750 patients with normal LV function undergoing angiography and PTCA randomized to quinapril vs. placebo and followed 3 yrs for cardiac end points	Primary end point was progression vs. nonprogression of disease, as defined by QCA or by a cardiac event. There was no apparent effect of quinapril on the progression of coronary atherosclerosis vs. placebo. However a number of questions have been brought up regarding this trial and more research may be warranted. For example, the dose may have been too low. Measurement of ACE activity or ACE II levels may be necessary to establish required doses.[47] Compliance rate for meds was 97.4% for quinapril and 98.8% for placebo. 15.4% of the quinapril group received lipid lowering meds from primary docs vs. 16% of the placebo group.
Ramipril, placebo	**APRES** trial[48] Prospective RCT to evaluate effect of invasive revascularization and ACE inhibitor tx in pts with angina pectoris and asymptomatic LV dysfunction 159 patients randomized to ramipril or placebo following revascularization	Mean follow-up: 33 months Reduction in risk of triple endpoint (cardiac death, AMI, clinical heart failure): 58% (95% CI 7-80%; p=0.031) Reduction in risk of quadruple endpoint (cardiac death, AMI, clinical heart failure, recurrent angina pectoris) not altered with ramipril

Other Factors

Other factors include: pharmacological and pharmacokinetic characteristics, patent expiration, provider preference, clinical practice guideline recommendations, dosing/administration, compliance/convenience issues, current usage/formulary status, and the existence of blanket purchase agreements, incentive price agreements, or contracts.

Pharmacology

- Angiotensin converting enzyme (ACE) converts angiotensin I to angiotensin II, a potent vasoconstrictor that increases vascular resistance, afterload, and blood pressure. Angiotensin II also directly stimulates aldosterone secretion from the adrenal cortex, increasing sodium and water reabsorption from the distal tubules, and activates the sympathetic nervous system, increasing norepinephrine release. ACE is widely distributed in the body, particularly in vascular endothelium, but also in kidney, gastrointestinal tract, testes, brain, plasma, and cerebrospinal fluid.
- In addition ACE—also known as kininase II—degrades bradykinin, which mediates release of local vasodilators (e.g., nitric oxide, epoprostenol, and platelet activating factor), which reduces peripheral vascular resistance. Kinins are normally rapidly degraded by kininase II in the lung and on the luminal surface of the endothelial cell membrane. While the contribution of bradykinin accumulation to the pharmacologic effects of ACE inhibitors is controversial, it is likely that both inhibition of angiotensin II production and accumulation of bradykinin contribute to the beneficial effects of ACE inhibitors.
- Because the potency of ACE inhibitors appears to be largely determined by the strength of binding of the zinc ligand and by the number of auxiliary binding sites, the recent discovery of two active binding sites in the ACE protein may be significant in regard to ACE inhibitor binding and selectivity. The clinical significance of different binding affinities is unknown. Peak serum concentrations of ACE inhibitors do not necessarily correlate with peak hypotensive effect, nor does inhibition of plasma ACE correlate with peak hypotensive effect or the duration of effect.
- The concentration of an ACE inhibitor in a particular tissue depends on the chemical characteristics of the ACE inhibitor (e.g., molecular size, ionization coefficient, lipophilicity), as well as the presence of blood-tissue barriers and the ability of the tissue to transform inactive prodrugs into active form. The presence of local renin-angiotensin systems in various organs implies that ACE inhibitors might differ in their ability to inhibit tissue ACE because of differences in tissue penetration. Due to differences in the degree of tissue ACE inhibition among species, animal studies cannot be easily extrapolated to humans. In vitro studies have noted difference in the degree of ACE inhibition in various tissues after two doses of ramipril[49] and a lower rate of disassociation from heart ACE for quinapril than lisinopril or enalaprilat.[50] There is no evidence that differences in tissue concentrations among various ACE inhibitors result in clinically significant differences in therapeutic effect or patient outcomes.
- A number of ACE inhibitors are available as ester prodrugs designed to improve gastrointestinal absorption. Formation of active diacid metabolites is largely in the liver, but may also occur in the gastrointestinal tract, extravascular tissue, and kidney.

Pharmacokinetics

Table 12: Pharmacokinetic Characteristics of ACE Inhibitors[a]

Drug	Onset / Duration (Hrs)	Protein Binding	Effect Of Food On Absorption	Active Metabolite	Half-Life (Hrs)[B]	Elimination
Benazepril	1/24	>95%	none	benazeprilat	10 - 11	renal
Captopril	0.25/ dose related	25-30%	reduced	none	< 2	renal
Enalapril	1/24	NA	none	enalaprilat	11	renal
Fosinopril	1/24	approx 95%	none	fosinoprilat	12	renal/hepatic
Lisinopril	1/24	NA	none	none	12	renal
Moexipril	1/24	approx 50%	reduced	moexiprilat	12	renal/hepatic
Perindopril						
Quinapril	1/24	approx 97%	reduced[c]	quinaprilat	3	renal/hepatic
Ramipril	1 - 2/24	approx 56%	reduced[d]	ramiprilat	13 - 17	renal/hepatic
Trandolapril	1/24	80%	none	trandolaprilat	16	renal/hepatic

a Table adapted from VA ACE inhibitor review and package insert for perindopril.
b Half-life reflects active metabolite when appropriate; accumulation half-life reported
c Rate and extent of absorption decreases moderately (25-30%) with a meal high in fat; clinical relevance unclear
d Rate of absorption reduced, not extent

Patent Expirations

Table 13: Patent Expirations

Generic Name	Trade Name	Generic Available	Manufacturer, Patent Expiration
Benazepril	Lotensin®	No	Norvartis; Aug 2003
Captopril	Capoten®	Yes	BMS & Various; Feb 1996
Enalapril	Vasotec®	No, but availability of multiple generics anticipated shortly after patent expires in August 00. Prices are expected to be low.	Merck; August 22, 2000
Fosinopril	Monopril®	No	BMS; Dec 2002
Lisinopril	Zestril®, /Prinivil® (branded products, AB-rated to each other)	No	Zeneca; Dec 2001 Merck; Dec 2001
Moexipril	Univasc®	No	Schwarz Pharma; Feb 2007
Quinapril	Accupril®	No	Pfizer/Warner Lambert; Aug 2001
Perindopril	Aceon®	No	Solvay; August 2006
Ramipril	Altace®	No	King Pharma; Jan 2005
Trandolapril	Mavik®	No	Knoll Pharma; June 2007

Provider Preference/Expert Opinion – Most of the providers contacted for this review had no strong preferences among ACE inhibitors, with many commenting that "an ACE is an ACE." Specific replies from Surgeon General consultants included:

- (Cardiology) – "Quinapril/ramipril look best in the lab – may be beneficial to add if the cost is comparable to others."
- (Cardiology) – "I think the literature is quite good about the preventive aspects of Altace <ramipril> in CV disease."
- (Nephrology) – "Fosinopril" <reason not given>
- (Nephrology) – "Lisinopril or fosinopril"
- (Internal Medicine) – "no strong feelings"
- (Internal Medicine) – "Don't have strong feelings on the once-daily ACEI's. They are all around 15 cents per day Government price, and flat priced."

WHMC staff cardiologist:

> "I have only reviewed the HOPE abstract to date. However, it looks very promising. My initial take is that it would be very good to consider switching to Ramipril if costs allow. A couple of my staff are real hot on introducing Ramipril."

WHMC staff IMC (talking about HOPE trial but regarding ACE inhibitors as class effect):

> "Excellent study. Of course they saw significant benefit in this population of >9000 high risk patients (80% had CAD, 38% with DM, 46% with HTN, 66% HLP, 43% with PVD). As compared to the CAPPP trial (Lancet 1999; 353: 611-16) which showed no benefit and a ? of increased risk of non-fatal CVA with captopril (this was a poorly done study in low risk patients (only 5-6% DM and only 8-9% CAD), the HOPE trial showed benefit even in patients who had controlled BP's to begin with (avg 139/79). This beneficial effect is likely multifactorial->vascular remodeling effects (dec vasc sm mm prolif, improved endothelial fxn, regression of LVH, ?even enhancing fibrinolysis) + dec complications from DM and dec incidence of DM to boot. CAPPP trial also demonstrated marked benefit in DM and decreased incidence of DM on ACEi->?improved insulin sensitivity, improved blood flow to pancreas, dec in hepatic insulin clearance, less abdominal obesity.
>
> The bottom line is that ACEi should also strongly be considered in CAD and other ASVD even in those with controlled BP in addition to the accepted indications for therapy (CHF, DM, non-DM nephropathy, post-MI)."

Clinical Practice Guideline Recommendations – DoD/VA Clinical Practice Guidelines for Hypertension and Diabetes do not recommend any specific ACE inhibitor.

Dosing and Administration

Table 14: Dosing (according to package labeling)

Generic	Trade name	Dosage Forms	Usual Dose* (Usual Target Dose)	Renal Adjustment	Comments
Benazepril	Lotensin	5, 10, 20, 40mg tabs	**HTN:** 10 mg qd (10-40 mg qd or divided bid) **CHF:** 5 mg qd (20mg qd)	Yes CrCl < 30 mL/min	
Enalapril	Vasotec	2.5, 5, 10 20mg tabs	**HTN:** 5mg qd (10-40 mg qd or divided bid) **CHF** 5 mg bid (5-10mg bid) **ALVD:** 2.5 mg bid (10mg bid)	Yes CrCl < 30 mL/min	
Fosinopril	Monopril	10, 20, 40mg tabs	**HTN:** 10 mg qd (20-40mg qd or divided bid) **CHF:** 10 mg qd (20 mg qd)	no	
Lisinopril	Zestril	2.5, 5, 10, 20, 30, 40mg tabs	**HTN:** 10 mg qd (10-40 mg qd) **CHF:** 5mg qd (20 mg qd) **Post-MI:** 5 mg initially; 5 mg 24 hrs; 10 mg 48 hrs (10-20 mg qd)	Yes CrCl < 30 mL/min	
Moexipril	Univasc	7.5, 15mg tabs	**HTN:** 7.5 mg qd (7.5-15 mg qd or divided bid)	Yes CrCl < 40 mL/min	Should be given 1 hour prior to meals on an empty stomach
Perindopril	Aceon	2, 4, 8 mg tabs	**HTN:** 4 mg qd (4-8 mg qd or divided bid)	Yes Safety not established with CrCl < 30 mL/min; 2 mg qd starting dose with CrCl > 30 mL/min	
Quinapril	Accupril	5, 10, 20, 40mg tabs	**HTN:** 10 or 20 mg qd (20-40 mg qd or divided bid) **CHF:** 5 mg bid (10-20 mg bid)	Yes CrCl < 30 mL/min	
Ramipril	Altace	1.25, 2.5, 5, 10mg caps	**HTN:** 2.5 mg qd (2.5-20 mg qd or divided bid) **CHF:** 2.5 mg bid (5 mg bid)	Yes CrCl < 40 mL/min	Capsules may be opened and sprinkled on applesauce or mixed with orange juice or water. Should be given 1 hour prior to meals on an empty stomach
Trandolapril	Mavik	1, 2, 4mg tabs	**HTN:** (whites) – 1mg qd (African Americans) – 2 mg qd (2 - 4mg qd) **Post-MI:** 1 mg qd (4 mg qd)	Yes CrCl < 30 mL/min	Only ACE inhibitor with FDA approved dosing recommendations in the African American population

HTN = hypertension; CHF = congestive heart failure; ALVD = Asymptomatic Left Ventricular Dysfunction

* Because African Americans are considered low renin producers, higher doses may be needed to see a therapeutic response in this population.

Compliance/Convenience Issues

- A major compliance issue is once-daily vs. BID dosing. It is probably fair to assume that, all other things being equal, a once-daily drug is preferable to a BID drug in terms of patient convenience and the likelihood that the patient will remember to take all doses of the medication. However, the difference in compliance between once daily and twice daily dosing of antihypertensives is clearly not as great a difference as that between BID and TID or QID dosing.
- Drugs with trough:peak ratios > 50% following once daily dosing (as measured by ambulatory blood pressure monitoring) are believed to give a more consistent blood pressure lowering effect. ACE inhibitors with trough: peak ratios > 50% include: enalapril, lisinopril, trandolapril and fosinopril. Drugs with a trough:peak ratio < 50% may require BID dosing for blood pressure control, which may affect patient compliance. ACE inhibitors with trough: peak ratios < 50% include: captopril, benazepril, perindopril, ramipril and quinapril.[51] However, many hypertensive patients will still do well on these meds with once daily dosing.
- The need for BID dosing with a given ACE inhibitor would affect not only patient compliance, but dosing distribution and total cost of treatment. This will be taken into account when price quotes for the ACE inhibitors are evaluated.
- An additional convenience issue is the availability of dosing formulation suitable for pediatric patients and patients unable to swallow tablets or capsules (e.g., patients receiving medication via feeding tubes) or the ease of compounding extemporaneous solutions suitable for such use. None of the ACE inhibitors are available in liquid form; however, ramipril capsules may be opened and mixed with beverages or applesauce.

Current Usage/Formulary Status

- In the simplest terms, choosing an agent with wide formulary acceptance and wide current usage means that there is a smaller probability that patients will be switched from another ACE inhibitor to the selected agent. The following is a survey of 55 Air Force pharmacies concerning formulary status of ACE inhibitors at their institutions. Fosinopril appears on 19/55 , benazepril on 14/55, quinapril on 7/55, ramipril on 1/55.

Table 15: Results of Survey of 55 USAF MTF pharmacies

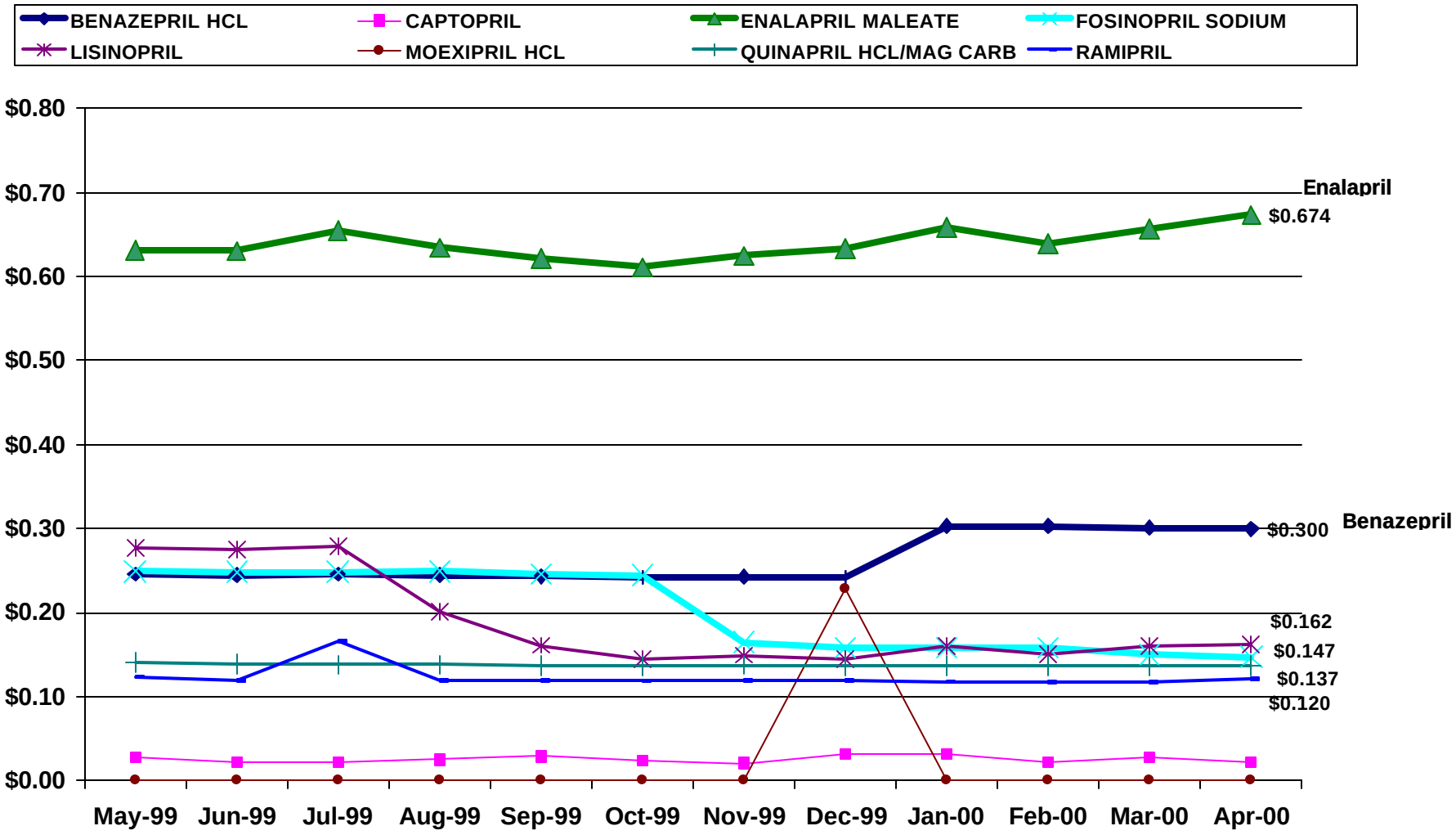
ACE I on MTF formulary	# of MTFs
BCF only	19
BCF + fosinopril	14
BCF + benazepril	11
BCF + quinapril	6
BCF + fosinopril + benazepril	2
BCF + fosinopril + ramipril	1
BCF + fosinopril + quinapril	1
BCF + fosinopril + benazepril + benazepril/HCTZ	1

- MTFs are unlikely to switch patients en masse from lisinopril to a new BCF agent, since lisinopril has a large existing market share and will remain on the BCF. However, MTFs may prefer the new agent to lisinopril and encourage its use if a large cost disparity exists. MTF *are* likely to switch at least some patients currently receiving agents other than lisinopril, especially if a large cost disparity exists or if the MTF wants to decrease the number of ACE inhibitors available on its formulary.
- Attached graphs include:
  - Average cost per tablet or capsule
  - Percent of total tablets

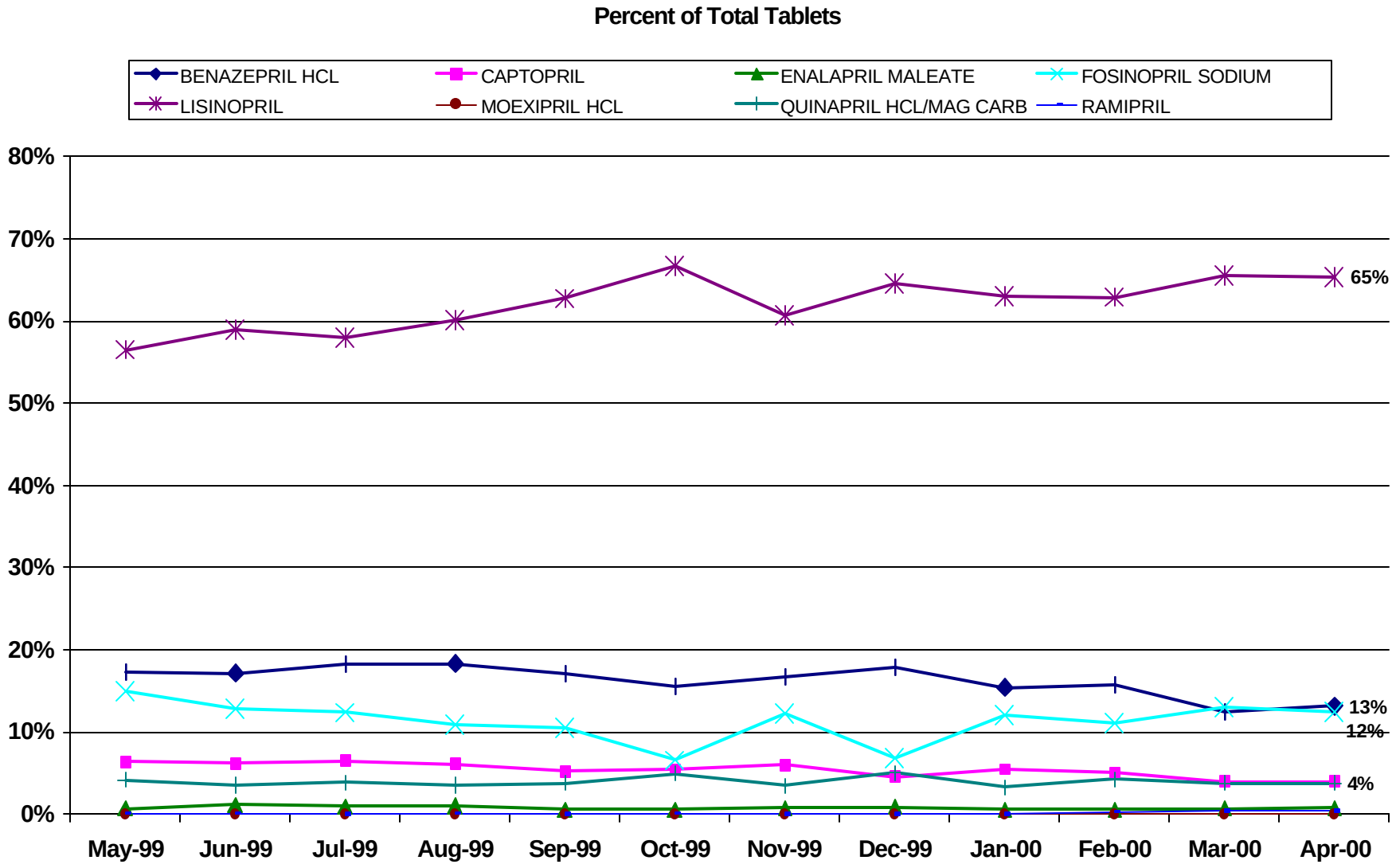
Blanket Purchase Agreements/Incentive Agreements/Contracts for ACE Inhibitors

- Aside from the contracts for captopril and lisinopril, the manufacturers of benazepril offer DoD MTFs an incentive agreement for Lotensin (benazepril) and Lotensin HCT (benazepril/hydrochlorothiazide). While selection of an agent other than benazepril for the BCF would not necessarily cause this agreement to be withdrawn by the manufacturer, the possibility exists. The number of facilities participating in the agreement is unknown.

Average Cost Per Tablet/Capsule



Source: DoD Prime Vendor purchase data. Average cost per tablet for moexipril is $0 for all months except Dec 99 because no moexipril was purchased in these months.


Percent of Total Tablets
BENAZEPRIL HCL
CAPTOPRIL
ENALAPRIL MALEATE
FOSINOPRIL SODIUM
LISINOPRIL
MOEXIPRIL HCL
QUINAPRIL HCL/MAG CARB
RAMIPRIL
80%
70%
60%
50%
40%
30%
20%
10%
0%
May-99
Jun-99
Jul-99
Aug-99
Sep-99
Oct-99
Nov-99
Dec-99
Jan-00
Feb-00
Mar-00
Apr-00
65%
13%
12%
4%

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